

DETAILED ACTION

Claims pending 1-7, 9-12, 15, 16, 24-33, 35-87 are pending.

Response to applicant's arguments:-

The arguments are based on that the applicants think that the examiner has not performed a balancing test but has merely asserted that the claims are just a routine experimentation of what is disclosed in US '767 patent.

This is incorrect.

The '767 patent does not teach away but teaches the various solvents and its effect on the polymorphs. The rejection is a 103 not a 102. There are several solvents tested. According to applicants own admission on page 3 of the specifications.

"U.S. Pat. No. 6,506,767 discloses two polymorphic forms of desloratadine, labelled Forms I and II (syn. form 1 and form 2). The XRPD peaks and the FTIR spectrum for the forms are also disclosed in the '767 patent.

The '767 patent discloses: "Surprisingly we discovered that certain alcoholic solvents, e.g., hexanol and methanol produced 100% polymorph form 1, but others, e.g., 3-methyl-1-butanol and cyclohexanol produced significant amounts of form 2. Chlorinated solvents, e.g., dichloromethane produced form 1 substantially free of form 2 but the compounds were discolored. Ether solvents such as dioxane produced form 1 substantially free of form 2 but other alkane ethers,, e.g., di-isopropyl ether produced. form 1 with significant amounts of form 2 and di-n-butyl ether favored formation of form 2. Ketones such as methyl isobutyl ketone produced crystalline polymorph form 1 essentially free of form 2 but methyl butyl ketone produced a 8:1 ratio of form 1 to form 2. Use of methyl isobutyl ketone is preferred to produce crystalline polymorph form 1 essentially free of form 2. Only ethyl acetate and di-n-butyl ether were found to produce crystalline polymorph form 2 substantially free of form 1. Use of di-n-butyl ether is preferred for producing crystalline form 2 substantially free of form 1."

The '767 patent, in Examples 1-3, prepares Form I by crystallization out of methyl isobutyl ketone, while in examples 4 and 5, prepares Form II by crystallization out of ethyl acetate and di-n-butyl ether, respectively.

The '767 patent also carried out stability tests on Polymorph Form I. According to the '767 patent, Form I was "subjected to stability testing at various temperatures (25, 30 and

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40°C) and relative humidities of 60%, 60% and 75%, respectively...No significant change (1%) from initial sample % form I and related compounds was observed."

The '767 patent warns against using polymorphic mixtures of desloratadine for formulation. According to the '767 patent, "such a mixture could lead to production of a [desloratadine] which would exist as a variable mixture of variable composition (i.e., variable percent amounts of polymorphs) having variable physical properties, a situation unacceptable in view of stringent GMP requirements." "

The US'767 patent discloses several solvents. Including the solvents that are used by the applicants, such as the chlorinated solvents, isopropyl ether and so on.) . The art of making polymorphs is in varying the conditions, solvents, temp. see Chong Hui, 2001, Stephen Byrn and also Guillory 1992. (cited in the previous O.A.)

A person skilled in the art would have known the routine experimentation that is required to make polymorphs and would be motivated to try, with an expectation of success.

Applicants examples 5-7 uses the same solvents as given in '767, chlorinated solvent (chloroform, isopropyl ether and so on) . Limitation of claim 6 and 7 is also met in US'767 patent. See column 10 and 11.

Also

Although Schumacher et al. disclose drying said mixture (column 10; column 11; column 12, lines 1-8), Schumacher et al. do not explicitly disclose a particular amount of residual organic solvent inherently present within said mixture, and also it does not disclose the actual % of form I and II that may have been inherently made .

See *In re Aller*, 105 USPQ 233, 235 (CCPA 1955). "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in

a disclosed set of percentage ranges is the optimum combination of percentages." See e.g., MPEP § 2144.06 and *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Schumacher et al. further disclose descarboxyloratine (a.k.a., desloratadine) prepared as a mixture of polymorphs of the free base from hexane (column 4, lines 1-4). Schumacher et al. further disclose that mixtures of desloratadine Form I and Form II are known and have been prepared (column 4, lines 5-6 and 18-22).

Thus with the state of the art in which various solvents and temperatures and conditions, seeding, grinding are routine methods of making polymorphs, it is obvious that a person of skill in the art would be motivated to make the various changes to obtain the mixtures or form I and form II.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). From the teachings of the references, it is clear that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. *KSR v Teleflex*.

According to the Rationales given in the *KSR v Teleflex* ruling see below

Rationales

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "Obvious to try"—choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill according to the (E) and (G) rationales, at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9-12, 15, 16, 24-33, 35-87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims state

- a) preparing a solution of desloratadine in a solvent selected from the group
- a) preparing a solution of desloratadine in ethyl acetate;
- a) preparing a solution of desloratadine in a C~ to C4 alcohol;
- a) preparing a solution of desloratadine in isopropanol,
and so on.

In the instant case where a specific form is made , it is not clear what the starting material form is. Is it a mixture to begin with or is it form I or form II. If so in what ratio.

All applicants claims state is that it is desloratadine. Thus the starting material itself can be form I and form II, or may be a pure form substantially free from the other. I which case applicants process is just tantamount to recrystallization.
Clarification is needed.

Claim Rejections - 35 USC § 102

Claims 1,4, 6, 7, 9, 15, 16, 24-27, are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 4,659,716 (hereinafter Villani et al.).

Villani et al. disclose recrystallization of 8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (a.k.a., desloratadine) from hexane (column 18, lines 5-6). And also THF, composition of Villani et al. would inherently possess the limitations of the instant claims because the desloratadine

mixture is formed according to instant Claim 1, 4, 10 Thus, Villani et al. fully anticipate all the limitations of the instant claims.

Claim Rejections. 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

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1. Claims 21-24, 26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,335,347 (hereinafter Gala et al.) in view of Villani et al.

Applicant claims:

The Applicant claims a process of making mixtures of crystalline Form I and Form II of desloratadine with different % s of form I and form II

Determination of the scope and content of the prior art

(MPEP 2141.01)

Gala et al. teach crystallization of loratadine from toluene, t-butyl methyl ether, heptane or mixtures thereof (column 3, lines 10-12). Gala et al. further teach pharmaceutical compositions comprising loratadine and inert pharmaceutically acceptable carriers (column 3, lines 64-65). Gala et al. also teach that both crystalline forms of loratadine have distinctly different physical properties (column 1, lines 48-50).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Gala et al. do not teach crystallization of desloratadine from toluene, heptane or mixtures thereof. However, Villani et al. teach that desloratadine is merely a structural derivative of loratadine, wherein desloratadine is prepared by decarboxylation of loratadine (column 2, lines 3-19).

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to crystallize desloratadine in toluene, heptane or mixtures thereof because Gala et al. teach crystallizing loratadine in toluene, heptane or mixtures thereof and Villani et al. teach that desloratadine is a structural derivative of loratadine and thus inherently obtain the mixtures of the forms of I and II.

The claims of the instant invention, would have been *prima facie* obvious for a person skilled in the art at the time of the instant invention to prepare the mixture of Form I and Form II of desloratadine using the same solvents because Gala et al. teach that the different forms of loratadine have different properties, and Villani et al. teach that desloratadine is a structural derivative of loratadine. Such would have been obvious in the absence of evidence to the contrary because it is generally *prima facie* obvious to use the same process or solvents to make the different mixtures. The idea of combining them flows logically from their having been taught

individually in the prior art. *In re Kerkhoven* 626 F.2d 646, 850, 205 USPQ 1069, 1072 (CCPA 1980).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10-12, 15, 16, 24-26 and 27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No.11447336. Although the conflicting claims are not identical, they are not patentably distinct from each other because The copending application claims are also drawn to a process of preparing a mixture of Form I and Form II of desloratadine. The same solvents

are used. See also the use of of hydrocarbon (claim 15.) This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 10-12, 15, 16, 24-26 and 27 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28-47 of copending Application No. 10/800291 Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to a process of making a mixture of Form I and form II using same solvent. The difference is that they are defined by other properties, however the instant claims can inherently have the same properties and absent any showing the claims are obvious .

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 1-7, 9-12, 15, 16, 24-33, 35-87 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rita J. Desai whose telephone number is 571-272-0684. The examiner can normally be reached on Monday - Friday, flex time..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Rita J. Desai/
Primary Examiner, Art Unit 1625

R.D.
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